# A New Simple Synthesis of 1,4-Benzodiazepines (1)



*T. Sugasawa, M. Adachi, T. Toyoda and K. Sasakura*

Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, 553 Japan

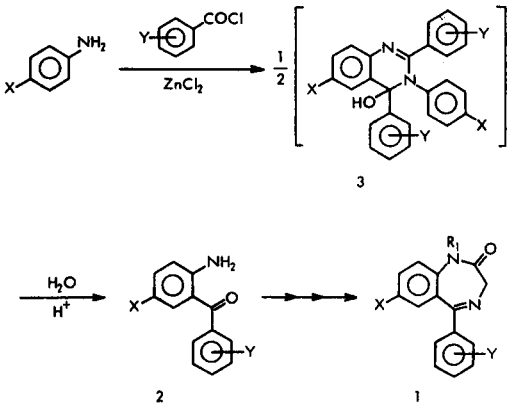
Received August 24, 1978

A convenient synthesis of 1,4-benzodiazepines starting from secondary-2-aminobenzhydrols, which are easily obtained from secondary anilines and benzaldehydes, is described. 7-Nitro-1-methyl-1,4-benzodiazepine **1d** can be formed from 5-nitro-2-methylaminomethylacylaminobenzophenone **10b** and **c** by using ammonium carbonate instead of ammonia, which gives only the Smiles-rearranged product **11**.

*J. Heterocyclic Chem.*, **16**, 445 (1979).

1,4-Benzodiazepines **1** have become a series of exciting drugs over the past ten years due to their tranquillizing effect. Thus, the synthesis of **1** has been investigated and established in detail (2a). Nevertheless, as pointed out by Sternbach himself, the only limiting factor in the preparation of **1** is the accessibility of 2-aminobenzophenones **2**, which are used as starting materials (2b). Compound **2** is prepared by treatment of *para*-substituted aniline with benzoylchloride in the presence of zinc chloride at 200 to 230°C followed by energetic hydrolysis of the intermediate **3**. Therefore, the yield of **2** is inevitably under 50% based on the aniline used (Scheme I).

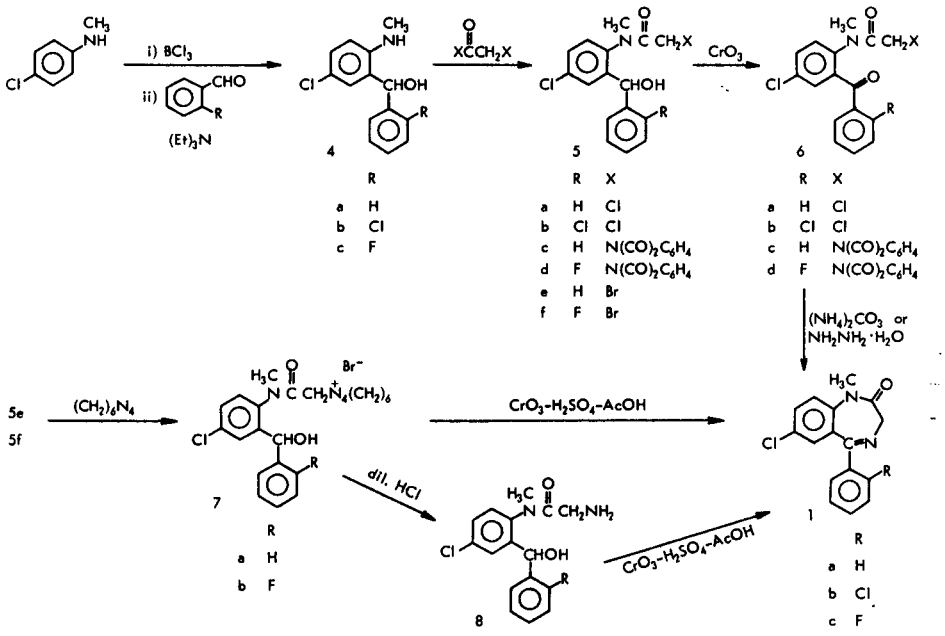
Scheme I



We describe here a new simple synthesis of **1** starting from *sec*-aminobenzhydrols **4**, which can be obtained in excellent yield by the specific *ortho*-hydroxybenzylation of *sec*-anilines *via sec*-anilinodichloroborane (3) as shown in Scheme II.

4-Chloro-2-methylaminobenzhydrols **4a**, **b** and **c** treated with haloacetylhalogenide or phthaloylglycylchloride under basic condition gave only the *N*-acylated compound **5** in excellent yield. Spectral and analytical data are shown in Table I.

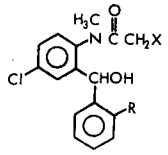
Scheme II



*0022-152X/79/030445-04$02.25*

Table I

Physical and Analytical Data of 2-Methylhaloacetamido- and 2-Methylphthaloylglycylamidobenzhydrols (5)



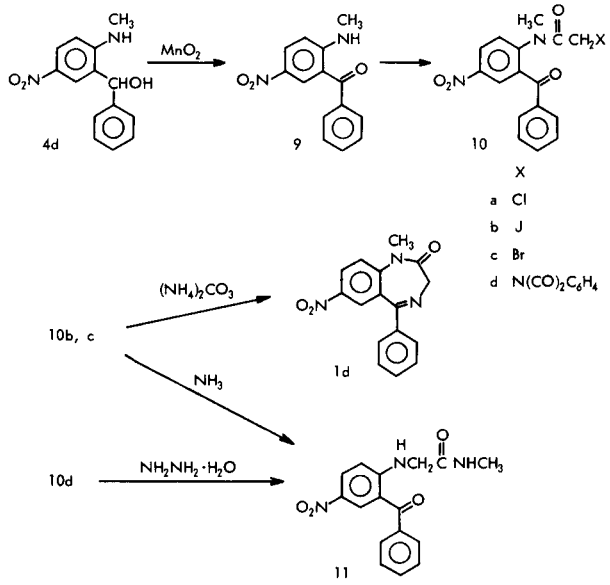
| Compound | R | X | M.p. °C | Ir ν Max Chloroform, $cm^{-1}$ | Analyses Calcd. Formula | Found |
|---|---|---|---|---|---|---|
| **5a** | H | Cl | Oil | 3610<br>1660 | | |
| **5b** | Cl | Cl | 146-147 (a) | 3595<br>3410<br>1666 | $C_{16}H_{14}NO_2Cl_3$<br>C 53.58<br>H 3.93<br>N 3.91<br>Cl 29.66 | <br>53.32<br>3.98<br>4.03<br>29.71 |
| **5c** | H | $N(CO)_2C_6H_4$ | 188-189 (a) | 3501<br>3475<br>1774<br>1721<br>1678 | $C_{24}H_{19}N_2O_4Cl$<br>C 66.28<br>H 4.40<br>N 6.44<br>Cl 8.15 | <br>66.07<br>4.52<br>6.21<br>8.29 |
| **5d** | F | $N(CO)_2C_6H_4$ | 172-173 (a) | 3470<br>1775<br>1719<br>1678 | $C_{24}H_{18}N_2O_4ClF$<br>C 63.65<br>H 4.01<br>N 6.19<br>Cl 7.83<br>F 4.20 | <br>63.51<br>4.41<br>6.19<br>7.76<br>4.25 |
| **5e** | H | Br | Oil | 3625<br>1665 | | |
| **5f** | F | Br | Oil | 3610<br>1665 | | |

(a) Recrystallized from dichloromethane-ether.

Compounds **5a**, **b**, **c** and **d** were oxidized to 2-aminobenzophenone **6** by Jones reagent. Compounds **6a** and **b** were converted directly to **1a** and **b** by treatment with ammonium carbonate in the presence of sodium iodide in acetonitrile at room temperature in comparable yield to that of the known method using liquid ammonia. Hydrazinolysis of **6d** gave **1c** in excellent yield. The yield of **1** by our process was almost double that by the known method (2a,b), based on the 4-chloro-aniline used (*ca.* 65%). Alternatively, **5e** and **f** were treated with hexamethylenetetramine giving the hexamethylenetetrammonium salts **7a** and **b**, which were converted directly to **1a** and **c**, respectively, by treatment with chromic anhydride under acidic condition (**7a** → **1a**) or by hydrolysis followed by oxidation (**7b** → crude **8** → **1c**).

Our synthetic method for **1** using 2-methylaminobenzhydrols **4** proved especially useful when the 7-nitro-derivative **1d** (4,6) was required. Namely, 5-nitro-2-methylaminobenzhydrol **4d** (3) was oxidized to the corresponding aminobenzophenone **9** (4) by manganese dioxide, which was converted to acylaminobenzophenone **10a** by the known method (5). Treatment of **10a** with sodium iodide followed by ammonium carbonate in dioxane at room temperature afforded the desired **1d** in excellent overall yield. It is very noteworthy that the use of ammonium carbonate gave **1d** (71% based on **4d**) with almost

Scheme III




negligible contamination by the Smiles-rearranged product **11** (7) (2%). Compound **11** was the sole product when **10c** was treated with ammonia (7) instead of ammonium carbonate or the imide **10d** was cleaved by aqueous hydrazine hydrate (8).

## EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected. Ir spectra were recorded in chloroform solution with a Koken DS-207B or JASCO IRS spectrophotometer. Nmr spectra were taken in deuteriochloroform solution on a Varian A-60 or T-60 spectrophotometer. Chemical shifts are expressed as δ values (parts per million) from tetramethylsilane. Column chromatography was conducted using silica gel (E. Merck, 70-230 mesh ASTM). Silica gel GF (E. Merck) was used for both analytical and preparative thin-layer chromatography (tlc).

5-Chloro-2-methylchloroacetamidobenzhydrol (**5a**) and 5-Chloro-2-methylchloroacetamido-2′-chlorobenzhydrol (**5b**).

To a stirred solution of chloroacetylchloride (251 mg., 2.02 mmoles) in dry ether (15 ml.) was added a solution of 4-chloro-2-methylbenzhydrol (**4a**) in dry ether (15 ml.) containing pyridine (0.163 ml., 2.02 mmoles) under ice-cooling and the solution was allowed to stand at room temperature for 2 hours. The precipitated pyridine hydrochloride was filtered off and the filtrate was washed with 2*N* hydrochloric acid and water. Drying and evaporation of the ether layer gave oily **5a** (655 mg., one spot on tlc; chloroform/ethyl acetate: 2/1). Compound **5b** was obtained by a similar procedure (87%).

5-Chloro-2-methylphthaloylglycylamidobenzhydrol (**5c**) and 5-Chloro-2-methylphthaloylglycylamido-2′-flurorbenzhydrol (**5d**).

To a stirred solution of phthaloylglycylchloride (470 mg., 2.09 mmoles) in dry ether (20 ml.) was added a solution of **4a** in dry ether (20 ml.) containing pyridine (0.17 ml., 2.09 mmoles) under ice-cooling and the solution was allowed to stand at room temperature for 2 hours. Dichloromethane was added and the organic layer was washed successively with 2*N* hydrochloric acid, 2*N* sodium bicarbonate solution and water. Drying and evaporation of the organic layer gave **5c** (88%). Compound **5d** was obtained by a similar procedure from 4-chloro-2-methylamino-2′-fluorobenzhydrol (**4c**) (10) (92%).

5-Chloro-2-methylchloroacetoamidobenzophenone (**6a**) (4) and 5-Chloro-2-methylchloroacetoamido-2′-chlorobenzophenone (**6b**).

To a stirred solution of **5a** (1.4 g., 4.04 mmoles) in acetone (3 ml.), Jones reagent [chromic anhydride (606 mg., 6.06 mmoles)] in acetone (25 ml.) was added under ice-cooling and the solution was allowed to stand for 5 minutes. To decompose the excess oxidant, isopropanol was added and the mixture was made alkaline with 1*N* sodium bicarbonate. The precipitate was filtered off on a celite layer and washed with dichloromethane. The combined filtrate was washed with water, dried and evaporated to give crude **6a**. Recrystallization from dichloromethane-ether gave **6a** (1.12 g., 86% based on **4a**, m.p. 122-123°, lit. (5) m.p. 123-124°). By a similar procedure, oily **6b** was obtained in 85% yield based on **4b**; ir (chloroform): 1675 $cm^{-1}$; nmr (deuteriochloroform): δ 3.12 and 3.42 (d, 3H, $NCH_3$), 3.90 and 4.03 (d, 2H, $CH_2$), 7.34-7.75 (m, 7H, aromatic protons).

7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**1a**) and 7-Chloro-1,3-dihydro-1-methyl-5-(2-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (**1b**).

A solution of **6a** (100 mg., 0.311 mmole) in acetonitrile (6 ml.) containing sodium iodide (47 mg., 0.311 mmole) and ammonium carbonate (400 mg.) was stirred at room temperature for 24 hours. The precipitate was filtered off and washed with dichloromethane. The combined filtrate was washed with water, dried and evaporated. The extract (88 mg.) was purified on tlc (dichloromethane/ethylacetate: 5/1) to give **1a** (5) (80 mg., 90%). Compound **1b** (5) was obtained by a similar procedure (82%).

5-Chloro-2-methylphthaloylglycylamidobenzophenone (**6c**) and 5-Chloro-2-methylphthaloylglycylamido-2′-fluorobenzophenone (**6d**).

Compound **5c** (100 mg.) was treated by a procedure similar to that used for **6a** from **5a** to give **6c** (92 mg., 92%, m.p. 177-178°; from dichloromethane-ethanol, lit. (9), m.p. 190-191°; from methanol, other crystal modification, m.p. 170-171°); ir (chloroform): 1782, 1725, 1690 (sh), 1680 $cm^{-1}$. Compound **6d** was obtained analogously to the above (91%). m.p. 117-119° (dichloromethane-ether); ir (chloroform): 1777, 1723, 1678 $cm^{-1}$; nmr: δ 3.08 (3H, s, $NCH_3$), 4.16 and 4.25 (2H, d, $CH_2$), 6.95 - 8.01 (m, 11H, aromatic protons.

*Anal.* Calcd. for $C_{24}H_{16}ClN_2O_4F$: C, 63.93; H, 3.58; Cl, 7.87; N, 6.21; F, 4.21. Found: C, 64.01; H, 3.68; Cl, 7.85; N, 6.24; F, 4.21.

7-Chloro-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2*H*-1,4-benzodiazepine-2-one (**1c**).

A solution of **6d** (100 mg.) in 95% ethanol containing 85% hydrazine hydrate (0.032 ml.) was refluxed for 1.5 hours. After cooling, the precipitate was filtered off and washed with dichloromethane. Evaporation of the combined filtrate gave **1c** (5) (64 mg., 96%).

Compound **1a** from 5-Chloro-2-methylbromoacetoamidobenzhydrol (**5e**) *via* the Corresponding Hexamethylenetetrammonium Salt (**7a**) by Simultaneous Hydrolysis and Oxidation.

Compound **5e** was obtained from **4a** by treatment with bromo-

acetylbromide instead of chloroacetylchloride for **5a**. A solution of **5e** (200 mg.) in acetonitrile (10 ml.) containing hexamethylenetetramine (151 mg., 1.08 mmoles) was allowed to stand at room temperature for 17 hours. The separated **7a** was filtered off and washed with acetonitrile to give pure **7a** (190 mg., 69%, m.p. 189-191°); ir (nujol): 3480-3640 (broad), 3240, 3180, 1675 $cm^{-1}$.

*Anal.* Calcd. for $C_{22}H_{27}BrClN_5O_2$: C, 51.92; H, 5.35; Br, 15.71; Cl, 6.97; N, 13.76. Found: C, 51.69; H, 5.57; Br, 15.42; Cl, 6.95; N, 13.50.

A suspension of **7a** (170 mg., 0.334 mmole) in acetic acid (1.7 ml.) containing Jones reagent (1 g., 1.67 mmoles) was stirred at room temperature for 1 hour. Ice was added and the mixture was made alkaline with aq. ammonia then extracted with dichloromethane. Washing, drying and evaporation followed by purification of the extract on tlc (dichloromethane/ethylacetate: 5/1) gave **1a** (49mg., 35% over-all yield based on **4a**). Compound **1a** was obtained from **5a** by a procedure similar to the above in 41% over-all yield based on **4a**.

**1c** from 5-Chloro-2-methylbromoacetoamido-2′-fluorobenzhydrol (**5f**) *via* the Corresponding Hexamethylenetetrammonium Salt (**7b**) by Oxidation Subsequent to Hydrolysis.

Crude **5f** (290 mg.) obtained from **4c** (200 mg., 0.752 mmole) was converted to **7b** by a procedure similar to the above. Changes involved the use of dichloromethane instead of acetonitrile as the solvent. Hydrochloric acid (2*N*, 10 ml.) was added to the resulting mixture, which was then stirred at room temperature for 1.5 hours. The clear solution obtained was separated and the organic layer was extracted successively with 2*N* hydrochloric acid and water. The combined acidic layer was made alkaline with concentrated ammonia and extracted with dichloromethane. Washing with water, drying and evaporation of the organic layer gave crude **8** (247 mg.). To a stirred solution of crude **8** in acetic acid containing 5% of sulfuric acid (W/W) (5 ml.) was added a solution of chromic anhydride (243 mg., 2.43 mmoles) in water (0.25 ml.), and the mixture was stirred at room temperature for 15 minutes. Water and sodium bisulfite were added, and the mixture made alkaline with aqueous ammonia then extracted with dichloromethane. A similar workup for **1a** from **5e** gave **1c** (99 mg., 43% over-all yield based on **5f**).

5-Nitro-2-methylaminobenzophenone (**9**).

A mixture of **4d** (3) (400 mg., 1.55 mmoles) in acetone (40 ml.) containing Attenburrow manganese dioxide (2 g.) was stirred at room temperature for 1 hours. The precipitate was filtered off and the filtrate was evaporated. The residue was dissolved in chloroform and passed through a short silica gel layer. The eluate was evaporated to give **9** [375 mg., 95%, m.p. 166-167° (acetonitrile-petroleum ether), lit. (4) m.p. 159-161°].

5-Nitro-2-methylchloroacetamidobenzophenone (**10a**).

A solution of **9** (300 mg.) and chloroacetylchloride (265 mg.) in benzene (30 ml.) was refluxed for 17 hours. After evaporation of the solvent, the residue was dissolved in chloroform and passed through a silica-gel layer (8 g.) to give crude **10a** (400 mg.).

7-Nitro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**1d**).

A mixed solution of crude **10a** (1.05 g., 2.89 mmoles) and sodium iodide (0.52 g., 3.47 mmoles) in acetone (70 ml.) was refluxed for 20 minutes. The precipitated sodium chloride was filtered off and the filtrate was concentrated to give crude **10b** (1.15 g.). A suspension of **10b** (1.15 g.) and ammonium carbonate (4g.) in dried dioxane (100 ml.) was stirred at room temperature for 20 hours. The precipitate was filtered off and washed with dioxane. The combined filtrate was concentrated and the residue was chromatographed (silica gel 60 pre-packed column, size B, Merck, dichloromethane/ethyl acetate: 5/1 as eluant) to give **1d** (572 mg., 71%, m.p. 159-161°, dichloromethane-methanol, lit. (4) m.p. 156-157°), and **11** (20 mg., 2%, m.p. 256-257°, dichloromethane-ether, lit. (8) m.p. 250.5-251.5°).

## REFERENCES AND NOTES

(1) This paper was presented at the 98th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, April 1978 [Japanese unexamined patent publication No. 48682 (1977)].

(2a) G. A. Archer and L. H. Sternbach, *Chem. Rev.*, 755-758 (1968); (b) L. H. Sternbach, *Angew. Chem., Int. Ed. Engl.*, **10**, 34 (1971).

(3) T. Sugasawa, T. Toyoda, M. Adachi and K. Sasakura, *J. Am. Chem. Soc.*, **100**, 4842 (1978).

(4) L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, B. Sach and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963).

(5) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy and A. Stewpel, *J. Org. Chem.*, **27**, 3788 (1962).

(6) S. Inaba, K. Ishizumi, K. Mori and H. Yamamoto, *Chem. Pharm. Bull.*, **19**, 722 (1971).

(7) N. W. Gilman, P. Levitan and L. H. Sternbach, *J. Org. Chem.*, **38**, 373 (1973).

(8) K. Ishizumi, S. Inaba and H. Yamamoto, *Chem. Pharm. Bull.*, **20**, 592 (1972).

(9) Delmar, Netherlands Patent 6500,446; *Chem. Abstr.*, **64**, 5120 (1966).

(10) Compound **4c** was obtained from 4-chloro-2-methylaniline and 2-fluoro-benzaldehyde by the procedure described in lit. (2) (85%), m.p. 79-81° (chloroform-petroleum ether).